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# Macrocephaly, Facial Abnormalities, Disproportionate Tall Stature, and Mental Retardation—A Sib Observation

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**We report on two brothers with relatively short limbs, macrocephaly, high and narrow forehead, frontal upsweep of hairline, hypotelorism, broad but short ears, straight back, and mild hypermobility of all joints. Both were hypotonic neonatally and had developmental delay and behavior problems. Several of the manifestations were present in the father, too. A literature search failed to uncover any similar case. Am. J. Med. Genet. 70:312–314, 1997.** © 1997 Wiley-Liss, Inc.

**KEY WORDS: macrocephaly; short limbs; developmental delay; neonatal hypotonia; facial dysmorphism**

## INTRODUCTION

The presentation of familial cases with multiple congenital anomalies often is a challenge for clinical geneticists, especially when a known syndrome diagnosis seems elusive. We had the opportunity of assessing from birth two brothers, with neonatal hypotonia, later developmental delay, and an apparently unique constellation of anomalies. Their father resembled them to a large extent. A literature search for similar combinations of anomalies failed to yield a diagnosis. Here we report on the patients in detail and provide a review of the differential diagnosis.

## CLINICAL REPORT

The brothers were the only children of young, nonconsanguineous parents. The eldest patient M, was born at 40 weeks of gestation, after an uneventful pregnancy and delivery. Birth weight was 3,450 g (50th centile). Neonatally he had moderate hypotonia, but no major feeding problems. The hypotonia was of sufficient severity to necessitate consultation with a child neurologist and extensive additional investigations including muscle biopsy. No abnormalities were found. The hypotonia diminished gradually in the first year of life, and eventually his motor development was normal with sitting at 9 months and walking unaided on his first birthday. He appeared to have speech delay, and later on learning problems. Recent formal psychologic testing showed his performance IQ to be 90 and the verbal IQ 80. From 6 years on, he had progressive behavior problems, including aggressiveness, necessitating placement in a special care center for 4 years. The only major medical problem was febrile convulsions in childhood. During infancy and childhood, his height followed a centile just above P97, weight-compared-to-height followed P90, and skull circumference was on the P98.

Clinical evaluation at 11 years (Fig. 1) showed a heavily built, mildly retarded boy with a peculiar face: high and narrow forehead, frontal upsweep, the colour of frontal hair being somewhat lighter than the other, hypotelorism (inner canthal distance 2.6 cm [10th centile], outer canthal distance 7.2 cm [below the 3rd centile]), down-slanting palpebral fissures, broad ears, and a broad occiput. The intra-oral structures were normal. His thorax impressed as being long, he had a mild pectus excavatum, and a straight thoracic vertebral column. His limbs were short (at a height of 160 cm his span was 155 cm), but hands (total hand length 17.8 cm, [above the 97th centile]) and feet (total foot length 21.8 cm, [above the 98th centile]) were big. All joints showed a mild hypermobility. Skin was normal, without hyperlaxity or pigmentary defects.

The younger brother, patient K, was born at 43 weeks of gestation, weighing 4,650 g (97th centile). He also had neonatal hypotonia. His motor development was somewhat slow; he sat at 10 months, and walked at 17 months. The hypotonia diminished spontaneously. There was moderate general mental delay, for which he attended special schools. Formal psychologi-

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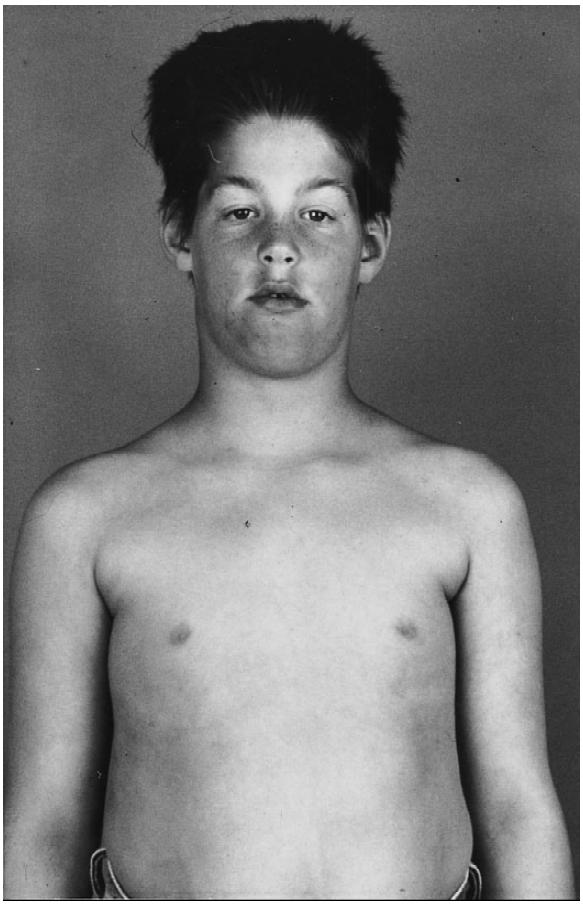

Fig. 1. Patient M at 11 years. Note high forehead, frontal upsweep, downward-slanted palpebral fissures, hypotelorism, and almost horizontal clavicles.

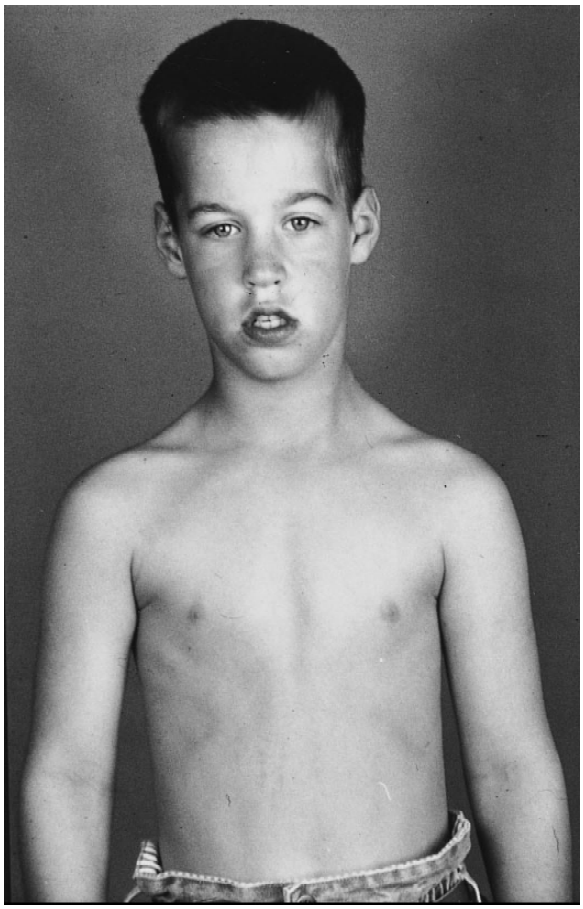

Fig. 2. Patient K at 8 years. Note striking resemblance to his brother.

cal testing showed an IQ of 65. The behavior problems were not as severe as in his brother, but seemed to increase with age. His medical problems were confined to chronic bronchitis. During infancy and childhood, his height followed the 75th centile, weight-compared-to-height P60, and he had a skull circumference 1 cm above P98.

Clinical evaluation at the age of 8 years (Fig. 2) showed that his facial traits were essentially identical to those of his brother. His thorax appeared even longer, and the shortness of limbs was also more pronounced (height 135.7 cm, span 124.8 cm). Hands (P80) and feet (P40) were of normal length.

The mother had a height of 169 cm (P50), a skull circumference of 57.0 cm (P80), no facial anomalies, and has had no learning problems. The father had a height of 178.8 cm (P40), arm span of 175 cm, and head circumference of 56.6 cm (P60). He resembled his sons by also having a high and narrow forehead, frontal upsweep, apparent hypotelorism (no formal measurements available), and downward slanted palpebral fissures (Fig. 3). He had a long thorax, and mild joint hypermobility. He had had mild learning and behavior problems as a boy. The father did not resemble his sibs, who were of normal intelligence, and stated that he resembled his deceased mother to a great extent (which was also evident in family pictures). Data on her mental status were unavailable. Several third- or fourth-degree relatives of the father were known with mild learning disabilities, but without behavior problems or

Fig. 3. Patient M and K together with their parents. Note high forehead with frontal narrowing, frontal upsweep, downward-slanted palpebral fissures, and hypotelorism in the father.

facial resemblance to the father. The father died at 39 years of paraproteinemia.

### Additional Investigations

Numerous investigations were undertaken to come to a definite diagnosis in the two brothers. These included plasma amino acids, urinary amino acids, organic acids, and mucopolysaccharide excretions, investigations for congenital infections (TORCH), karyotyping using high resolution banding techniques, and molecular studies for the fragile X syndrome, all with normal results in both patients. Results of neurologic investigations including EEG, EMG, muscle biopsy, and neuroradiology (CT scan in patient K, MRI in patient M) showed no abnormalities. Cardiologic investigations demonstrated a first grade atrioventricular block at age 6 years in patient M, but a more recent ECG was completely normal. Results of cardiologic studies in patient K were normal also. Both had normal hearing.

A complete radiological survey was performed in both patients and their father. In patient K bone age was normal, in patient M bone age was advanced by 18 months. The long bones in the limbs of all three relatives were equally shortened, without dysplasia. No other abnormalities were found.

TABLE I. Summary of the Clinical Findings in the Present Family

| | Patient M | Patient K | Father |
|---|---|---|---|
| Height (cm) | 160 | 136 | 179 |
| Arm span (cm) | 155 | 123 | 175 |
| Skull circumference[a] | P98 | >P98 | P60 |
| Neonatal hypotonia | + | ++ | ? |
| Developmental delay | + | ++ | +/– |
| Behavior problems | ++ | + | +/– |
| High and narrow forehead | + | + | + |
| Frontal upsweep | + | + | + |
| Broad occiput | + | + | + |
| Hypotelorism | + | + | + |
| Broad and short ears | + | + | – |
| Long-appearing thorax | +/– | + | + |
| Straight thoracic vertebral column | + | + | – |
| Joint hypermobility | + | + | +/– |

[a]In centiles.

## DISCUSSION

The main findings in the sibs and their father are summarized in Table I. Macrocephaly, short limbs, some of the facial findings, neonatal hypotonia, and developmental delay were described in 2 sibs by Winter et al. [1987]. However, these patients also had thoracic dysplasia with short ribs, metaphyseal dysplasia of long bones, communicating hydrocephaly, and in one of them, ataxia and hearing loss, which allows easy differentiation.

The neurofaciodigitorenal syndrome was described in 2 brothers [Freire-Maia et al., 1982], with macrocephaly, high forehead, mild ear dysplasia, congenital hypotonia, and developmental delay. However, these patients had a much more severe delay, and also had prenatal and postnatal growth retardation, and acrorenal field defects. The patients with neurofaciodigitorenal syndrome resembled FG syndrome, as do the present patients. They share the macrocephaly, tall forehead, cowlicks, congenital hypotonia with joint laxity, developmental delay and behavior problems [Romano et al., 1994]. Differences are that most patients with FG syndrome are more severely retarded, have most often short stature and no specific shortness of limbs, suffer from severe chronic constipation with or without anal anomalies, the joint laxity progresses to joint contractures, and often persistent fetal pads are found. Furthermore, the pattern of inheritance is X-linked recessive, while in the present family the findings are most compatible with autosomal dominant inheritance.

We conclude that it may be possible that the present patients have a hitherto undescribed condition. Because of similar findings in the father and possibly the paternal grandmother the pattern of inheritance may well be autosomal dominant.

## ACKNOWLEDGMENTS

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